

Unveiling the health implications of vitamin K2 deficiency

Tao Zhang^{1,*}

¹School of Food Science & Environmental Health, Technological University Dublin, Grangegorman, Dublin 7, D07 ADY7, Ireland

²The Trinity Centre for Natural Products Research, School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin 2, D02 PN40, Ireland

*Author for correspondence:
Email: tao.zhang@tudublin.ie

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Commentary

Zhang *et al.* provide an extensive review titled “Vitamin K2 in Health and Disease: A Clinical Perspective” [1], expanding on their earlier research [2]. Vitamin K (VK) is a crucial cofactor for the γ -carboxylation of glutamic acid residues in VK-dependent proteins (VKDPs). The human body contains at least 17 different VKDPs [3], also known as Gla proteins, which can be classified into hepatic and extra-hepatic VKDPs based on their location of synthesis within the body [4]. Hepatic VKDPs encompass coagulation factors II, VII, IX, and X, along with anticoagulant proteins C, S, and Z. Extra-hepatic VKDPs include osteocalcin, matrix Gla protein (MGP), Gla-rich protein (GRP), growth arrest-specific protein 6 (Gas6), proline-rich Gla proteins (PRGP1 and 2), transmembrane Gla proteins (TMG3 and TMG4), periostin, and the Gamma-Glutamyl Carboxylase (GGCX) enzyme [5]. Vitamin K2 (VK2) is more widely distributed and performs more physiological functions compared to vitamin K1 (VK1). VK2 is beneficial in preventing and managing cardiovascular diseases, neurological disorders, chronic kidney disease, cancers, liver diseases, obesity, improving bone development, lowering fracture risk, and boosting immune function [1,2]. This commentary focuses on the impact of insufficient VK2 levels in the body and the increased risk of various health conditions.

Osteoporosis

Osteoporosis is a systemic skeletal condition characterised by reduced bone mass and deterioration of bone tissue microarchitecture, leading to increased bone fragility, decreased bone strength, and a heightened risk of fractures. VK2 is crucial for promoting bone formation and inhibiting bone resorption, thus maintaining balanced bone metabolism. VK2 supports bone formation through the following mechanisms: (i) carboxylating γ -glutamic acid residues in osteocalcin, resulting in γ -carboxylated osteocalcin, which enhances calcium deposition and increases bone mineralisation rate [6]. Osteocalcin, also referred to as bone Gla protein (BGP), is predominantly synthesised by osteoblasts, odontoblasts, and certain proliferating chondrocytes, playing a significant role in bone calcium metabolism [7]; (ii) participating in steroid and xenobiotic receptor (SXR)-mediated transcriptional regulation, which upregulates the expression of genes associated with osteoblasts and the extracellular matrix, thereby enhancing collagen aggregation in bones [8].

VK2 also inhibits bone resorption through multiple mechanisms: (i) inhibiting the expression of cyclooxygenase-2 (COX-2) and consequently prostaglandin E2 (PGE2) synthesis, decreasing osteoclast activity and bone resorption [9]; (ii) suppressing the activation of bone resorption factors such as interleukin (IL)-1 α and nuclear factor kappa B (NF- κ B), thereby reducing bone resorption [10]; (iii) inducing apoptosis in osteoclasts and inhibiting the mRNA expression of lysosomal enzymes

(cathepsins) that are responsible for degrading the bone matrix [11]. Therefore, deficiency in VK2 can adversely impact bone metabolism, leading to the development of osteoporosis.

Cardiovascular Conditions

Vascular calcification is commonly associated with hypertension, atherosclerosis, diabetic vascular complications, vascular injury, chronic kidney disease (CKD), and aging, serving as a significant marker for atherosclerosis, stroke, and peripheral vascular diseases [12]. In end-stage renal disease (ESRD) patients, vascular calcification is an independent risk factor for cardiovascular disease [13]. Characterised by arterial stiffness and reduced compliance, vascular calcification can lead to myocardial ischemia, left ventricular hypertrophy, heart failure, and even thrombosis.

As a coenzyme for γ -glutamyl carboxylase, VK2 is critical for the carboxylation of osteocalcin produced by osteoblasts, forming γ -carboxyglutamate. This process captures Ca^{2+} ions from the blood, facilitating their deposition in bones and thereby preventing ectopic calcification in soft tissues and blood vessels. Deficiency in VK2 could lead to vascular calcification, increasing the risk of cardiovascular diseases [2]. Studies show that patients undergoing maintenance haemodialysis often exhibit significantly lower VK2 levels, indicating widespread deficiency in this group [14-16].

Besides osteocalcin, other VKDPs such as MGP and Gas6 are vital in inhibiting vascular calcification [17]. MGP, primarily produced by chondrocytes and arterial wall cells, is essential in preventing vascular calcification [18]. Gas6, found in various organs, contributes to inflammatory responses, homeostasis, and functions in the cardiovascular, nervous, urinary systems, as well as tumorigenesis [3]. Research indicates VK1 has little effect on vascular calcification, suggesting VK2 deficiency primarily decreases the activity of calcification inhibitors like MGP and Gas6 [19]. Therefore, VK2 is important for both bone and vascular health, playing an essential role in the prevention and management of atherosclerosis and hypertension.

Additionally, VK2 deficiency could lead to bleeding disorders. VK deficiency bleeding can manifest in various locations, with early-onset bleeding often presenting as head hematomas and typical neonatal bleeding as gastrointestinal haemorrhage [20]. Late-onset bleeding frequently manifests as intracranial haemorrhage, the most severe clinical consequence of VK deficiency and a major cause of infant mortality and disability [21].

Obesity and Diabetes

Diabetes is a significant global health issue, and recent research has uncovered several ways in which VK, particularly VK2, influences insulin resistance and glucose metabolism: (i) both carboxylated and uncarboxylated forms of osteocalcin are integral to glucose metabolism [22]. Supplementing with osteocalcin can reverse insulin resistance and hyperglycemia caused by osteocalcin gene deletion in mice [23]. Clinical studies have shown a negative correlation between serum total osteocalcin levels and fasting blood glucose, insulin levels, and other glucose metabolism indicators such as HOMA-IR [24-26]. VK2 supplementation has been found to boost osteocalcin levels and alleviates insulin resistance in people with type-2 diabetes [27]; (ii) VK2 reduces insulin resistance through its anti-inflammatory effects. Elevated levels of inflammatory markers, including tumour necrosis factor-alpha (TNF- α), IL-6,

and C-reactive protein (CRP), are associated with insulin resistance [28-30]; (iii) VK2 regulates lipid metabolism by lowering total plasma cholesterol, fat accumulation, and triglyceride levels [31]. Increased total cholesterol and low-density lipoprotein cholesterol, coupled with decreased high-density lipoprotein cholesterol, are linked to visceral fat accumulation, which is associated with insulin resistance and impaired glucose metabolism [32,33]. Both animal and human studies have indicated that VK2 supplementation could reduce lipid levels, including cholesterol and visceral fat [31,34,35]. Additionally, elevated intracellular VK2 levels could downregulate VKORC1L1, a gene encoding VK epoxide reductase, thus inhibiting preadipocyte differentiation and influencing overall fat and glucose metabolism [36]. Ultimately, deficiency in VK2 may disrupt lipid and glucose metabolism, increasing the risk of obesity and diabetes. This highlights the importance of adequate VK2 levels for supporting metabolic health and preventing related diseases.

Liver Health

The liver, the body's largest metabolic organ, has extraordinary regenerative abilities. In acute liver injury, liver progenitor cells, known as oval cells, are crucial for orchestrating repair [37]. Chronic liver damage is often observed in patients who have undergone partial hepatectomy in clinical settings [38], during which the activation of hepatic progenitor cells (oval cells) can promote liver recovery. In fact, oval cells appear in large numbers around liver lobules when the liver suffers severe damage or the proliferation of mature hepatocytes is compromised [39]. During liver regeneration, oval cells produce Matrilin-2, an extracellular matrix protein essential for forming the hepatic basement membrane [40]. Studies have shown that VK2 effectively stimulates the proliferation of oval cells and enhances Matrilin-2 expression in a 2-AAF/PH rat model (2-acetylaminofluorene administration followed by a 2/3 partial hepatectomy). This stimulation promotes liver regeneration [41]. As a result, deficiency in VK2 could impair liver regeneration and increase susceptibility to liver damage, highlighting VK2's critical role in maintaining liver health and preventing injury.

Increased Cancer Risk

VK2 has also been shown to promote apoptosis in tumour cells through various mechanisms [2,42,43]: (i) VK2 activates protein kinases, regulating the activity of various transcription factors and inhibiting the small G protein Rho. Rho, highly expressed in several malignant tumours, is closely associated with tumour growth, invasion, and metastasis. By inhibiting Rho, VK2 induces tumour cell apoptosis; (ii) VK2 induces apoptosis in tumour cells by activating caspase-3, downregulating Bcl-2, upregulating Bax, and enhancing c-myc expression; (iii) the naphthoquinone structure of VK2 leads to ROS generation, causing intracellular glutathione depletion and subsequent tumour cell apoptosis.

VK2 deficiency is linked to an increased risk of hepatocellular carcinoma (HCC), characterised by high levels of hepatoma-derived growth factor (HDGF), which promotes the proliferation of HCC cells. VK2 has been observed to inhibit HCC cells by suppressing HDGF and significantly decreasing its protein expression, while also inducing cancer cell differentiation by modulating connexin gene expression [44]. Additionally, VK2 suppresses the transcription and translation of fibroblast growth factor receptor 3 (FGFR3), which is overexpressed in HCC cells, thereby inhibiting their proliferation [45].

Moreover, VK2 can also induce the apoptosis of leukaemia cells. Research has indicated that VK2 could significantly induce apoptosis in NB4 leukaemia cells in a time- and concentration-dependent manner [46]. VK2 selectively induces apoptosis in myeloid leukaemia cells but does not have this effect on normal bone marrow cells or lymphoid leukaemia cells, consistent with clinical observations that VK2 does not cause bone marrow suppression [47]. Furthermore, VK2 also promotes apoptosis and G0/G1 cell cycle arrest in chronic myeloid leukaemia K562 cells [48] and triple negative breast cancer cells [49].

For this reason, deficiency in VK2 may increase the risk of developing various cancers, including HCC and leukaemia, underlining VK2's critical role in cancer prevention and treatment.

Neurological Disorders

VK2 is essential for sphingolipid synthesis and is the primary active form of VK in the brain [1]. Its protective effects, particularly against inflammation and oxidative stress, are well-documented [50,51]. Research indicates that VK2 may offer therapeutic benefits for neurological disorders associated with VK2 deficiency, including Alzheimer's disease, stroke, and Parkinson's disease [52,53].

The brain is the organ most sensitive to hypoxia. Therefore, cell damage and necrosis caused by local brain tissue hypoxia are the pathological basis for the occurrence and development of various brain diseases. Hypoxia in brain tissue causes abnormal activation of glial cells, among which astrocytes are the most predominant glial cells in the central nervous system. Their response plays a crucial role in the outcome of hypoxic brain injury. The brain is particularly sensitive to hypoxia, which can cause cellular damage and necrosis, contributing to the development and progression of various neurological conditions. During hypoxic events, glial cells, especially astrocytes - key support cells in the central nervous system—become abnormally activated, playing a crucial role in the outcomes of hypoxic brain injury. Studies have shown that VK2 significantly enhances astrocyte activity under hypoxic conditions while reducing reactive oxygen species (ROS) and superoxide levels. This protective effect is believed to be associated with the mitochondrial quality-control loop and the involvement of VKDPs such as Gas6 [54,55]. Henceforth, deficiency in VK2 may increase susceptibility to neurological disorders, highlighting the importance of maintaining adequate VK2 levels for brain health and the prevention of neurological diseases.

Gut Microbiota Imbalance

The gut microbiota ecosystem, comprising microbial communities, epithelial cells, intestinal secretions, and nutrients, is pivotal for human health, with the gut microbiota being the most significant component [56]. The equilibrium of these microbial communities is crucial for various health functions, including nutrient breakdown and metabolism, enhanced digestion and absorption, defence against pathogenic invasions, maintenance of intestinal barrier integrity, and regulation of the immune system [57]. Gut bacteria are a primary source of endogenous VK2 in the human body, and the growth and activity of the gut microbiota are closely linked to VK2 metabolism levels [58]. Consequently, VK2 is essential for maintaining the homeostasis of the gut microenvironment. Deficiency in VK2 could disrupt the metabolic balance of the gut microbiota, resulting in potential health outcomes.

Other Diseases

VK2 deficiency may contribute to several other health conditions, including:

Chronic kidney disease (CKD)

Deficiency in VK2 could result in elevated dephosphorylated-uncarboxylated MGP (dp-ucMGP) levels, associated with kidney damage. High dp-ucMGP levels are an important cardiovascular risk marker in CKD patients [59]. Research indicates that oral VK2 supplementation significantly enhances VKDP carboxylation in non-dialysis CKD patients, reducing dp-ucMGP levels and decreasing kidney damage and cardiovascular risk [14].

Rheumatoid arthritis (RA)

VK2 has been found to inhibit the proliferation of fibroblast-like synoviocytes and progression of collagen-induced arthritis [60]. Given the significant role of synovial hyperplasia in the pathogenesis of RA, VK2 may be effective in reducing synovial inflammation and potentially slowing the progression of RA.

Acute lung injury (ALI)

In vivo studies have demonstrated VK2's significant protective effects against ALI. VK2 reduces inflammation and apoptosis through the inhibition of P38 MAPK signalling and ferroptosis [61]. Additionally, VK2 alleviates mitochondrial dysfunction, reduces Ca²⁺ overload, and inhibits excessive autophagy [62]. These findings emphasise VK2's potential as a novel therapeutic candidate for ALI by mitigating LPS-induced pathological changes and supporting lung recovery.

Atopic dermatitis (AD)

Immune dysregulation is key in AD. Research indicates that VK2 could inhibit the proliferation of mitogen-activated peripheral blood mononuclear cells (PBMCs) in AD patients [63], a function not significantly affected by VK1 [64]. Moreover, VK2 substantially reduces CD4⁺ and CD4⁺CD25⁺ cells in PBMCs, suggesting VK2 may help treat AD by modulating T cell function in these patients [64].

Conclusion

In conclusion, deficiency in VK2 is linked to an increased risk of several diseases. Maintaining adequate VK2 levels is crucial for reducing the risk and severity of these conditions, emphasising VK2's importance in overall health and disease prevention.

Conflicts of Interests

The author has no conflicts of interest to declare.

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